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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/051,013	10/09/1998	TIMOTHY H. BESTOR	48075-B-PCT	7512

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/051,013	BESTOR, TIMOTHY H.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 34-47* is/are pending in the application.

4a) Of the above claim(s) *16,17,19-23,34-41 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,18,24-26 and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

[1] Claims 1-26 and 34-47 are pending in the application.

[2] Applicant's cancellation of claim 29 and amendment to claims 1-3, 6, and 12-15 in Paper No. 21, filed March 03, 2003, is acknowledged.

[3] Claims 16, 17, 19-23, 34-41, and 47 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention (claims 34-41 and 47) or species (claims 16, 17, and 19-23), there being no allowable generic or linking claim.

[4] Claims 1-15, 18, 24-26, and 42-46 are being examined on the merits.

[5] Applicant's arguments filed in Paper No. 21 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, Second Paragraph

[7] The rejection of claim 9 under 35 USC 112, second paragraph, as being indefinite in the recitation of "a pLS vector" is maintained for the reasons of record and the reasons stated below. Applicant argues (page 4 of Paper No. 21) the examiner acknowledges that the specification contains a diagram (Figure 6) of a pLS vector and therefore, a skilled artisan would know the features required for a pLS vector. Applicant's argument is not found persuasive. While Figure 6 provides a diagram of a pLS vector, providing minimal descriptive elements of the vector, a skilled artisan would not recognize the features of the unidentified regions of the vector. Based on the diagram, it appears there are substantial regions of the vector that are undefined and a skilled artisan would not recognize the sequence that is present in those regions. As such, a skilled artisan would not recognize those features required for a pLS vector.

Claim Rejections - 35 USC § 112, First Paragraph

[8] The written description rejection of claims 1-15, 18, 24-26, and 42-46 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 4 of Paper No. 19). Applicant argues (beginning at page 5 of Paper No. 21) the specification provides written description for the entire genus of chimeric proteins and encoding nucleic acids are described in the specification. Applicant argues that it is unnecessary to describe the structures of all possible species of chimeric proteins to establish written description. Applicant argues that all that is required is a representative number of such chimeric proteins and asserts that a representative number of examples, their design, and selection have been disclosed in the specification. Applicant argues the examiner has stated that two representative examples of chimeric proteins have been disclosed and applicant further cites pages of the specification that allegedly describe in sufficient detail methods for design, selection, and affinity maturation of other chimeric proteins. Beginning at the bottom of page 7 of Paper No. 21, applicant argues that no structure/function relationship be established to adequately describe the invention. Applicant argues that it is sufficient for written description that applicant has provided working examples and has allegedly described how to make the chimeric proteins without undue experimentation. Applicant argues that the text of *UC California v. Eli Lilly*, (43 USPQ2d 1398) quoted by the examiner is inapplicable to the instant rejection as it relates to claims to genetic material unique to a given species or class, and not to chimeric proteins such as those claimed here. Applicant's arguments are not found persuasive. It is noted that some of applicant's arguments address the enablement rejection and not the instant written description rejection. As such, the examiner has responded to applicant's arguments only to the extent those arguments address the written description rejection. The examiner maintains his position that the specification fails to adequately describe the entire genus of chimeric proteins or encoding nucleic acids. Regarding applicant's assertions that a structure/function relationship is not required to adequately describe the invention and the text of *UC California v. Eli Lilly*, (43 USPQ2d 1398) quoted by the examiner is

inapplicable to the instant rejection, it is noted that structures of the components of the chimeric protein are an essential feature of the claimed invention and should therefore have adequate description in the specification, which they do not. In fact, the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, state that the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number* of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov. The examiner acknowledges that only a *representative number* of species of the entire genus of chimeric proteins or encoding nucleic acids is necessary to satisfy the written description requirement. However, the specification fails to provide such a representative number of species, particularly the structures of such species. The examiner stated that (in the scope of enablement rejection and not the written description rejection) two working examples of chimeric proteins have been disclosed in the specification under Example 3 at pages 44-45 of the instant specification. It is noted that these working examples are merely prophetic examples and provide no description of relevant identifying characteristics sufficient to describe either of the components of the genus of chimeric proteins or encoding nucleic acids. In this case, the function of the first component of the chimeric protein is described – a DNA methyltransferase with attenuated DNA binding activity and the function of the second component is described – a DNA binding protein that binds to a gene's promoter. However, the specification fails to describe any structural features of either of the components of the chimeric protein. The chimeric protein encompasses a genus of variant DNA methyltransferase polypeptides with attenuated DNA binding activity while maintaining methyltransferase activity and a genus of DNA binding proteins that bind to any gene's promoter. One of skill in the art would recognize that the structures of

the genus of variant DNA methyltransferases and DNA binding proteins is highly variant as there is no common structural feature possessed by members of the genera. Because the genus of variant DNA methyltransferases and DNA binding proteins is highly variant and the specification fails to provide any structure or relevant identifying characteristics sufficient to show possession, the specification fails to adequately describe the claimed genus of chimeric proteins and encoding nucleic acids. In this case, more evidence is required to show possession of the entire genus of chimeric proteins and encoding nucleic acids.

[8] The enablement rejection of claims 1-15, 18, 24-26, and 42-46 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 5 of Paper No. 19). Applicant argues (beginning at page 8 of Paper No. 21) the specification enables the claimed invention. Beginning at the middle of page 9 of Paper No. 21, applicant argues the breadth of claims 1-6, 11-14, 18, 24-26, and 44-46 is relatively narrow. Applicant's argument is not found persuasive. It is the examiner's position that the specification fails to enable the claimed invention. For example, claim 1 encompasses a chimeric protein for inhibiting gene expression by methylation of a methylation site within a promoter comprising two components. The first component being any DNA methyltransferase having any variation resulting in attenuated DNA binding activity while maintaining methyltransferase activity and the second component being any DNA binding protein that binds to any gene's promoter – including promoters yet to be identified. The scope of the claims is, contrary to applicant's assertion, not narrow, but is *overly broad in scope* and is not enabled by the instant specification.

Beginning at the bottom of page 9 of Paper No. 21, applicant argues the specification provides adequate guidance for making the entire scope of the claimed invention. Applicant's argument is not found persuasive. The specification fails to provide the necessary guidance for making the claimed invention. The working examples provided by the specification are mostly prophetic and fail to provide even a single specific mutation in a DNA methyltransferase that would result in attenuated DNA binding while maintaining methyltransferase activity. Furthermore, the specification fails to provide guidance

regarding DNA binding proteins that would bind to any desired promoter. A skilled artisan recognizes that the structure of a DNA binding protein will determine its ability to bind a specific promoter sequence and guidance is therefore required to direct a skilled artisan to those promoters that will bind a given promoter sequence. Such guidance has not been provided.

Beginning at the top of page 10 of Paper No. 21, applicant argues isolation of proteins or encoding nucleic acids with altered functionality is not highly unpredictable. Applicant argues that the specification teaches how to make the chimeric proteins. Applicant argues the examiner's citing of the specification in showing such unpredictability of mutations (page 40, lines 10-11) is incorrect as this statement allegedly does not relate to unpredictability in generating mutants, but relates to using random mutagenesis. Applicant argues the examiner's citing of the specification providing support for unpredictability in obtaining the desired mutant (page 42, lines 4-7) does not corroborate unpredictability, but is a statement as to the amount of routine experimentation that is required. Applicant argues that a large quantity of experimentation does not indicate a non-enabling disclosure so long as such experimentation is not undue. Applicant's argument is not found persuasive. Due to the broad scope of the claims and the complete lack of guidance and working examples provided in the specification, there exists a high degree of unpredictability for making the claimed invention. It is again noted that applicant states that one cannot predict which mutations will result in the desired reduction in DNA binding affinity of a DNA methyltransferase (page 40, lines 10-11). While this statement was provided as a prelude to the necessity of using random mutagenesis, it nonetheless provides evidence of the unpredictability for generating the desired DNA methyltransferase variant(s). Furthermore, a skilled artisan would recognize that this unpredictability is compounded by the necessity for not only generating a variant DNA methyltransferase with attenuated DNA binding activity, but also having maintained the ability to methylate DNA as is required to inhibit gene expression. While random mutagenesis is used widely in the art, a skilled artisan would have no way of predicting whether the application of this method to any DNA methyltransferase to generate a variant with attenuated DNA binding activity with the ability to methylate DNA would be successful. As the name indicates – it is random and not specific and so a

skilled artisan would recognize the high degree of unpredictability in obtaining the desired variant. Furthermore, as this method is completely random, a large amount of experimentation may be necessary to obtain – if at all possible - the desired mutant, as acknowledged by applicant (page 42, lines 4-7). Since this method is completely random and applicant has provided no specific mutations that will guide a skilled artisan for making the desired variant, a skilled artisan would recognize the large amount of experimentation required to make the invention.

Beginning at the top of page 11 of Paper No. 21, applicant argues the pharmaceutical composition of claims 44-46 is enabled as the examiner has not provided evidence that would support a position of lack of enablement for these claims. Applicant's argument is not found persuasive. It appears applicant has disregarded the examiner's statements regarding a lack of enabling disclosure for the claimed "pharmaceutical composition". The specification clearly fails to teach how to make and use the claimed "pharmaceutical composition". As stated in a previous Office action (see pages 8 and 9 of Paper No. 19),

> "It is unpredictable what diseases can be effectively treated using a 'pharmaceutical composition' comprising a vector of claim 7 encoding a chimeric protein of claim 1. Neither the specification nor the prior art provide sufficient guidance as to what specific diseases could be successfully treated by administering a 'pharmaceutical composition' comprising said vector, and attempting to identify a disease treatable using such a 'pharmaceutical composition' would constitute undue experimentation. While the specification provides in vitro experimental results that suggest that a *specific* chimeric protein inhibits gene expression from a *specific* promoter (see Examples 4-7 beginning at page 47 of the instant specification), the specification provides no indication that the claimed chimeric proteins as broadly claimed or even the specific chimeric proteins as disclosed in Examples 4-7 would have any use in treating a disease state beyond mere speculation. The art recognizes the clinical significance of DNA methylation for treatment of diseases involved in aberrant gene expression, e.g., cancer. Singal et al. (*Blood* 93:4059-4070) teach '[s]elective modulation of DNA methylation may therefore have important clinical implications for the prevention and treatment of cancer' (page 4067). However, the art also recognizes the unpredictability that exists as the technology remains immature. Singal et al. teach '[t]o develop safe and effective strategies for therapeutic alteration of DNA methylation, the factors that regulate the specificity of both the methylation and demethylation processes must be more fully understood' and that 'understanding the factors involved in DNA methylation-induced gene silencing will facilitate attempts to selectively affect gene expression' (page 4067). Furthermore, even if the specification had provided sufficient guidance as to a disease treatable by administering a 'pharmaceutical composition' comprising said vector, the specification provides no guidance as to what, besides said vector, would compose such a composition. Making and testing the infinite number of compositions to find one that is

> effective would constitute undue experimentation. Therefore, the specification fails to enable one of ordinary skill in the art how to make and/or use the 'pharmaceutical composition' encompassed by the claims."

This evidence clearly supports a position of lack of enablement for the claimed "pharmaceutical composition".

[9] The enablement rejection of claim 9 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 6 of Paper No. 19). Applicant argues (page 11 of Paper No. 21) the specification contains a diagram of a pLS vector. Applicant argues the making of DNA vectors is routine and that a skilled artisan would know how to make and use a pLS from the diagram provided in Figure 6 in view of what is known in the art without undue experimentation. Applicant's argument is not found persuasive. As stated in item 7 above, the diagram of a pLS vector of Figure 6 omits significant portions of the vector. As such, a skilled artisan would not know how to make a pLS vector, even in view of what is known in the art. As portions of the vector are completely undefined, a skilled artisan would recognize the unpredictability in assigning the nucleic acid sequence of the omitted portions of a pLS vector of Figure 6. The specification does not provide a repeatable method for making the vector and the vector does not appear to be readily available to the public. The claimed vector sequence is not fully disclosed, nor has the sequence required for its construction been shown to be publicly known and freely available. As stated in a previous Office action, the enablement requirements of 35 U.S.C. § 112, first paragraph may be satisfied by a deposit of the vector. Accordingly, it is deemed that a deposit of the vector should have been made in accordance with 37 CFR 1.801-1.809.

Conclusion

[10] All claims are rejected. No claim is in condition for allowance.

[11] Claims 1-15, 18, 24-26, and 42-46 would appear to be allowable if rewritten to overcome the objection(s) and/or rejection(s) under 35 U.S.C. 112, first and second paragraphs, set forth in this Office action.

[12] The examiner requests that applicant provide a copy of all pending claims in the response to this Office action.

Applicant's amendment to claim 15 necessitated inclusion of this claim in the rejections under 35 USC 112, first paragraph. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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Patent Examiner
Art Unit 1652

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